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Clinical Observations after Radiotherapy with Re-Irradiation of Diffuse Intrinsic Pontine Glioma in Childhood - Clinical Case with Literature Review

Lena Marinova*, Vaska Vassileva, Iliya Gabrovski, Galin Vulchev and Viktor Petrov

Medical Oncology Clinic, Department of Radiation Oncology and Metabolic Brachytherapy UMHAT "Queen Joanna" Sofia, Bulgaria.

***Correspondence:**
Lena Marinova, Medical Oncology Clinic, Department of Radiation Oncology and Metabolic Brachytherapy UMHAT "Queen Joanna" Sofia, Bulgaria.

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ABSTRACT

Diffuse intrinsic pontine glioma (DIPG) is an aggressive primary pediatric brain tumor. Despite the application of various curative methods, including radiotherapy (RT) with or without chemotherapy (Ch), targeted agents and immunological approaches, there is no achievement of clear improvement in median overall or progression-free survival (PFS).

We present a 6-year-old girl with DIPG after a 3 D conformal radiotherapy (3D CRT) in the brain stem tumor with a 1.5 cm insurance zone, by three fractions gradually rising daily doses (DD) 1,6 Gy -1,8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to total dose (TD) 33 Gy. The sum of total tumor dose is 38.6 Gy, corresponding to a biological equivalent dose to 2 Gy/ equieffective dose (EQD2) 46.71 Gy. After 8 months, due to local tumor progression, local tumor re-irradiation up to TD 20 Gy with DD 2 Gy was performed. In children with rapidly enhancing neurological symptoms and worsened forecast, it is appropriate to carry out hypophractionated RT up to 45 Gy with DD 3 Gy in 15 fractions, which achieves PFS similar to conventional fractionated RT.

Our observations from the realized RT are that despite highly risky tumor localization, hypophractionated RT is well tolerated, without acute neurological toxicity and allows second irradiation / re-irradiation, due to local tumor progression.

Keywords

Diffuse intrinsic pontine glioma, Childhood, Hypofractionated Radiotherapy, Re-irradiation, Progression-free survival.

Introduction

Diffuse intrinsic pontine glioma (DIPG) is the most aggressive primary pediatric brain tumor [1], which is diagnosed almost exclusively among children with a median age of 6 to 7 years [2-5]. A diagnosis of DIPG carries a dismal prognosis, with a 2-year survival rate of <10%, making this brain tumor one of the most fatal pediatric malignancies [6,7]. DIPG is an extremely aggressive brain tumor with the median survival <1 year, for which curative therapy is unavailable [8]. Most patients have a rapidly progressive and fatal course and usually die within 18 months after diagnosis [4]. Radiation therapy (RT) is considered an aggressive palliative therapy, because it prolongs survival by a mean of 3–6 months [9]. We present DIPG in a 6-year-old girl after hypophractionated RT, followed by re-irradiation due to local tumor progression, in order to discuss the clinical observations and the benefit of RT to improve overall and progression-free survival with good quality of life.

Clinical Case

We present a 6-year-old girl. In April 2021, the parents noticed speech and equilibrium difficulty, followed by subsequently headaches and episodic vomiting. On 14.05.2021, brain MRI was conducted, which visualized an infiltrate intraaxial lesion in the pontine brainstem, whose engaged structures were blended and

deformed. The tumor has dimensions 44x33x34mm. and high T2 signal intensity. A lightweight dilatation of both lateral ventricular and third cerebral ventricle without data on transependimal liquor resorption is recorded (Figure 1).

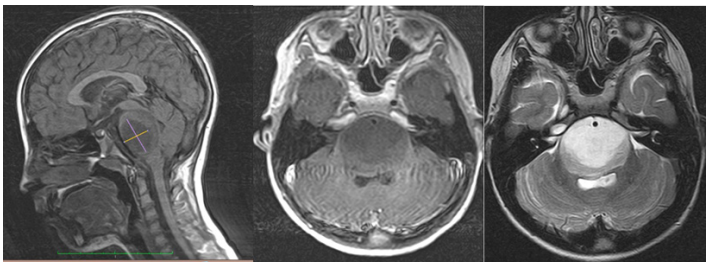

Figure 1: Brain MRI/14.05.2021 - An infiltrate intraaxial lesion in the pontine brainstem with high T2 signal intensity and dimensions 44x33x34mm.

After consultation with experienced neurosurgeons, it is considered diffuse infiltrative glioma in the pontine brainstem, which is inoperable and due to high risk, no biopsy is required. Oncology commission has assessed, that the only healing opportunity is to conduct a definitive radiotherapy (RT). In June / 2021, a 3 D conformal radiotherapy (3D CRT) in the brain stem tumor with a 1.5 cm insurance zone, by three fractions gradually rising daily doses (DD) 1,6 Gy -1,8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to total dose (TD) 33 Gy was conducted. The sum of total tumor dose is 38.6 Gy, corresponding to a biological equivalent dose to 2 Gy/ equieffective dose (EQD2) 46.71 Gy. The child endured RT very well, without acute neurological effects and no changes in laboratory performance. Figure 2 and Figure 3 present tumor volume contouring for reparation of forthcoming RT and 3D CRT with dose tumor distribution and dose in adjacent normal brain structures.

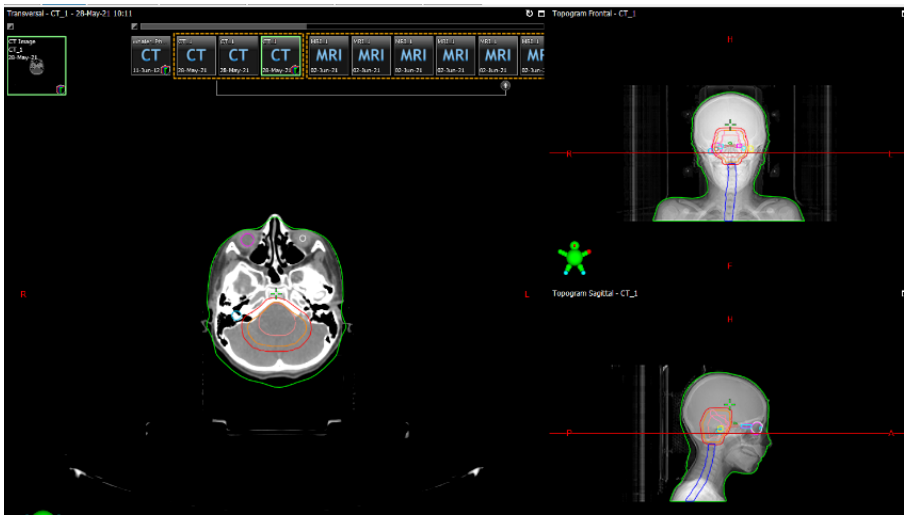

Figure 2: 3D conformal radiotherapy planning raying by contouring of the brainstem tumor volume and the adjacent normal tissues and organs.

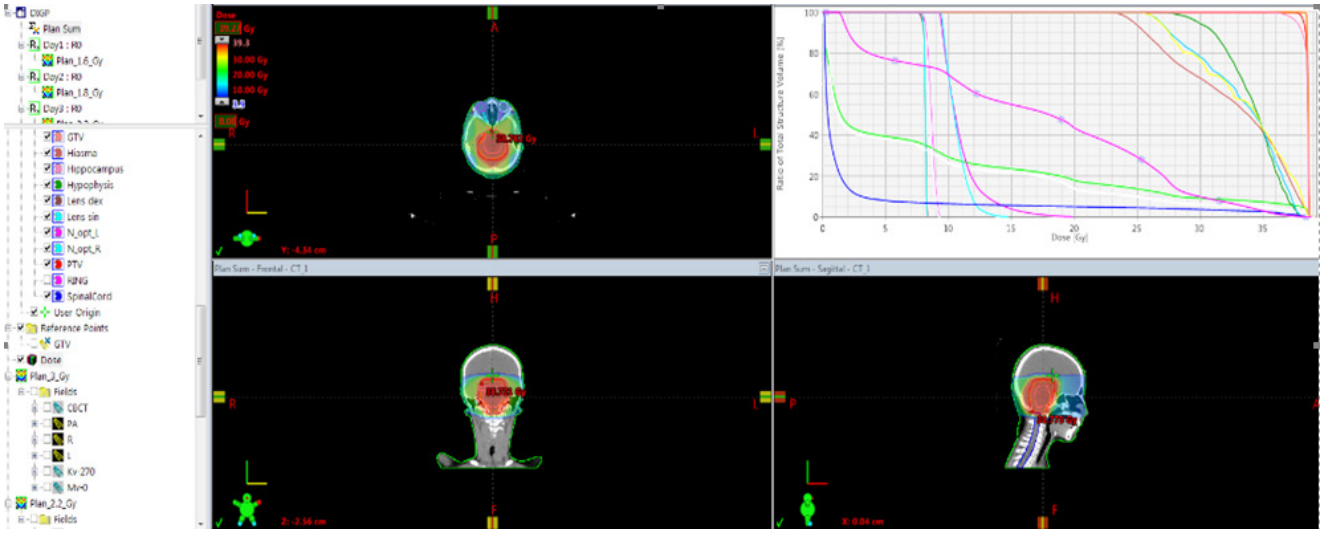

Figure 3: 3D Conformal Radiotherapy in the brainstem tumor by three fractions gradually rising DD 1,6 Gy -1,8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to TD 33 Gy/ biological equivalent dose to 2Gy/ equieffective dose (EQD2) 46.71 Gy. The histogram presents the distribution of radiation doses in the criticak adjacent normal tissues and in target volume.

After 8 months of completion of RT, on the brain MRT, a local tumor progression was established (Figure 4). Due to the lack of other alternative therapeutic methods, after a literary review, a re-irradiation was conducted. It was again Intensity modulated RT (IMRT) with VMAT technique in brain stem target volume with a 0.2 cm insurance zone with DD 2 Gy up tu TD 20 Gy (Figures 5,6). The child endured RT very well, without acute neurological effects and no changes in laboratory performance.

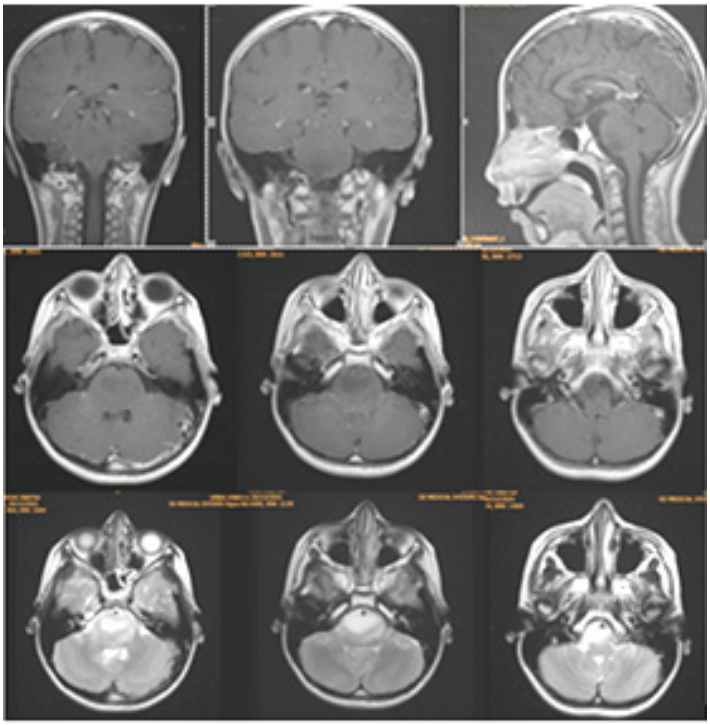

Figure 4: Brain MRI/ December 2021 Local tumor progression after 3D Conformal Radiotherapy with DD 1,6 Gy -1,8 Gy -2.2 Gy, followed by 11 fractions hypofractionated RT with DD 3 Gy up to TD 33 Gy/ biological equivalent dose to 2Gy/ equieffective dose (EQD2) 46.71Gy.

Discussion

The brainstem is the posterior stalk-like part of the brain that connects the cerebrum with the spinal cord [10]. It has the critical roles of regulating cardiac and respiratory function, helping to control heart rate and breathing rate [11]. The pontine nuclei are a collection of pontine motor nuclei in the anterior pons that have many connections with the cerebellum via the middle cerebellar peduncle and assist with coordinating movement and help to modulate breathing [12]. Because of these important vital functions of the brain stem, the brain tumors localized therein are extremely difficult to treat, especially with the application of the radiation method, which can cause a sudden stopping of respiratory and cardiac activity.

Surgery of DIPG to relieve hydrocephalus, is not indicated, because the typical appearances on MRI are characteristic and reduction in tumour bulk only adds to the child's worsened overall condition [13]. There is currently no indication for image guided stereotactic brain biopsy in children with a short history and typical MR appearances, because it currently will not alter management strategy [14]. During the past 3 decades numerous clinical trials have been conducted in newly diagnosed DIPG patients including radiotherapy with or without chemotherapy, targeted agents and immunological approaches. None of these trials have demonstrated a clear improvement in median overall or progression-free survival (PFS) [15]. Radiation remains the gold-standard treatment for diffuse intrinsic pontine gliomas (DIPG); by contrast, chemotherapy has not shown any benefit [16]. Several studies have concluded that conventional external-beam radiotherapy to a dose of 54 Gy in 30 fractions in 6 weeks is the mainstay of treatment [5,17-22] with median time to progression and overall survival of 6 and 9 months, respectively [21,23]. The current standard of treatment consists of conventionally fractionated RT to a range of 50.4–59.4 Gy in 28–33 fractions of 1.8 Gy daily, over 6 weeks, followed by the best supportive care [24]. Doses of radiation > 50 Gy are associated with improved survival compared with lower doses [25]. As a general principle, the treatment volume

Figure 5: Intensity modulated radiotherapy planning raying by contouring of the brainstem tumor volume and adjacent normal tissues and organs.

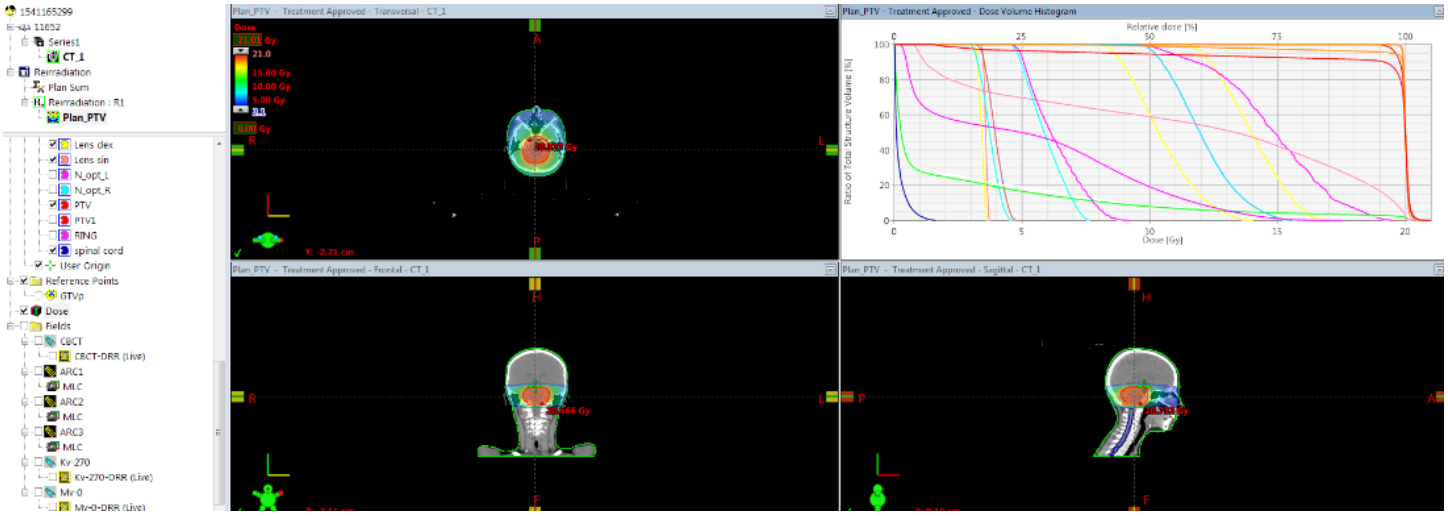

Figure 6: Intensity modulated RT (IMRT)/ re-irradiation with VMAT technique in brain stem target volume with a 0.2 cm insurance zone with DD 2 Gy up tu TD 20 Gy. The histogram presents the distribution of radiation doses in the criticak adjacent normal tissues and in target volume.

of the radiation field should encompass all the site(s) of disease with a defined margin to allow for non-imageable tumour spread into adjacent brain (1 cm for low grade and 2 cm for high grade tumours) [26]. To increase the overall and disease-free survival, other dose fractionation modes such as hyperfractionated and hypofractionated RT are applied [6,27]. Freeman et al. conducted a multiyear trial designed to assess the efficacy of sequentially escalated doses of hyperfractionated RT (66 Gy in 1.1 Gy fractions, 70.2 Gy in 1.17 Gy fractions, and 75.6 Gy in 1.26 Gy fractions; all twice daily in 60 fractions over 6 weeks) [28-30]. The conclusion is that, higher doses of hyperfractionated RT do not improve outcomes in DIPG. Given the paucity of data in favor of hyperfractionation schemes for DIPG, the potentially higher risks of acute toxicities, and the significant treatment burden associated with this approach [6]. Hypofractionated radiotherapy has potential radiobiological advantages over standard conventional fractionated therapy in newly diagnosed glioblastoma multiforme [31]. Some institutions have employed hypofractionated RT to decrease the length of therapy in an effort to reduce the patient's burden, with clinically similar levels of disease control reported [16,32-35]. In a retrospective study, Negretti et al./2011 treated with hypofractionated RT twenty-two children's DIPG with rapid neurological worsening, linked to worse prognosis. Twenty patients received photon at a dose of 45 Gy in 15 fractions of 3 Gy and two children at a dose of 60 Gy and 45 Gy combined photon and neutron. The median OS was 7.6 months (range: 0.3–21.0) and median PFS was 5.7 months (range: 1.4–15.8) [16]. In the Jannsens G.O. et al/ 2013 study, 27 patients conducted hypofractionated RT over 3 to 4 weeks with either 39 Gy in three Gy fractions (n = 16) or 44.8 Gy in 2.8 Gy fractions (n = 11). No significant difference in median OS (9.0 vs 9.4 months; $P = .8$) and time to progression (5.0 vs 7.6 months; $P = .2$) was observed between hypofractionated versus conventional RT, respectively [32]. Hypofractionated radiotherapy is well tolerated with the advantage of decreasing the treatment burden on children and their families [6], with nearly comparable results to conventional fractionation, though not fulfilling the non-inferiority assumption [35]. Due to the shorter healing period of the hypophractionated RT, we considered to realize it after gradually rising daily doses due to critical neurological structures localized in the brain trunk (Figures 2,3). Despite our concerns about the tolerability of this irradiation, the child endured it very well without acute side neurological toxicity.

Radiation therapy is essential in the definitive management of DIPG. With advances in treatment techniques, it is feasible to reirradiate select patients with progressive disease [36]. Alvaro Lassaletta et al. identified 16 patients with progressive DIPG who received re-irradiation (rRT). Median time from diagnosis to progression was 10.5 months. rRT was given focally in 14 patients at a dose ranging from 21.6 to 36 Gy. All patients died, with a median time from rRT to death of 6.48 months. When compared to a historic cohort of 46 consecutive patients, the median time from progression to death was 92 days in the non-reirradiated patients versus 218 days in the reirradiated ones ($P = 0.0001$) [37]. ReRT can safely be delivered for progressive diffuse intrinsic pontine glioma. Utility analysis suggests that a regimen of 24 Gy in 12 fractions is preferred [38]. At first progression, 31 children with DIPG, aged 2-16 years, underwent re-irradiation (dose 19.8-30.0 Gy) alone (n = 16) or combined with systemic therapy (n = 15). An interval of ≥3 months after upfront radiotherapy was required before re-irradiation. Clinical improvement with re-irradiation was observed in 24/31 (77%) patients. On multivariable analysis, interval to progression (corrected hazard ratio = .27-.54; P < .01) and re-irradiation (corrected hazard ratio = .18-.22; P < .01) remained prognostic for survival [39]. Zamora PL et al /2021 identified five patients with progressive DIPG who received re-irradiation. Re-irradiation was well tolerated with no serious adverse events reported and all patients experiencing stable to improved neurologic function during treatment. Median overall survival from time of diagnosis was 16.3 months, which is longer than the historical average of less than 12 months. Re-irradiation (rRT) for symptomatic relief is an option at disease progression [40]. A Spanish group reported two patients with diffuse intrinsic pontine glioma (DIPG) who received a second re-irradiation course

at second tumor progression [41]. The second child received 39 Gy in 13 fractions followed by anti-angiogenic therapy. This was followed by 20 Gy in 10 fractions approximately 11 months later. Afterwards, Irinotecan and Rapamycin were given. Eight months later, a second re-irradiation course with 20 Gy in 10 fractions with concomitant Temozolomide was administered with good tolerance and rapid clinical response. Survival was 1 year after second re-irradiation. The cumulative EQD2 was equivalent to 89 Gy in this case [41]. Based on the attempt of the above-mentioned authors, in the presented clinical case with tumor progression after 8 months of the hypophractional RT (Figure 4), we decided to carry out a re-irradiation in brain stem target volume with a 0.2 cm insurance zone with DD 2 Gy up tu TD 20 Gy (Figures 5,6). Despite our concerns about the tolerability of this re-irradiation, the child experienced it very well without acute side neurological toxicity.

Conclusion

Diffuse intrinsic pontine glioma (DIPG) is the most aggressive primary pediatric brain tumor. Despite the various combined healing approaches, the forecast is extremely unfavorable. Inputs inability to carry out a biopsy, as well as partial tumor resection, the primary healing method is radiotherapy, applied by different fractionation of the radiation dose. In children with rapidly enhancing neurological symptoms and worsened forecast, it is appropriate to carry out hypophractionated RT up to 45 Gy with DD 3 Gy in 15 fractions, which achieves PFS similar to conventional fractionated RT. Our observations from realized RT are that despite highly risky tumor localization, hypophractionated RT is well tolerated, without acute neurological toxicity and allows second irradiation / re-irradiation, due to local tumor progression after 8 months. The preferred radiation dose of re-irradiation is TD 20 Gy with DD 2 Gy, which is well tolerated, improves neurological symptoms and increases the child's survival with good quality of life.

References

1. Hashizume R. Epigenetic targeted therapy for diffuse intrinsic pontine glioma. Neurol Med Chir Tokyo. 2017; 57: 331-342.
2. Berger MS, Edwards MS, LaMasters D, et al. Pediatric brain stem tumors Radiographic pathological and clinical correlations. Neurosurgery. 1983; 12: 298-302.
3. Freeman CR, Farmer JP. Pediatric brain stem gliomas A review Int J Radiat Oncol Biol Phys. 1998; 40: 265-271.
4. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children Critical review of clinical trials. Lancet Oncol. 2006; 7: 241-248.
5. Littman P, Jarrett P, Bilaniuk LT. Pediatric brain stem gliomas. Cancer. 1980; 45: 2787-2792.
6. Matthew Gallitto, Stanislav Lazarev, Isaac Wasserman, et al. Role of Radiation Therapy in the Management of Diffuse Intrinsic Pontine Glioma A Systematic Review. Adv Radiat Oncol. 2019; 4: 520-531.
7. Maria BL, Rehder K, Eskin TA. Brainstem glioma I Pathology clinical features and therapy. J Child Neurol. 1993; 8: 112-128.
8. Jackson S, Patay Z, Howarth R, et al. Clinico-radiologic characteristics of long-term survivors of diffuse intrinsic pontine glioma. J Neurooncol. 2013; 114: 339-344.
9. Vanan MI, Eisenstat DD. DIPG in children - what can we learn from the past? Front. Oncol. 2015; 5: 237.
10. Vishram Singh. Textbook of Anatomy Head Neck and Brain. 20114; 3: 363.
11. Brainstem, Definition, Structure, et al. Encyclopedia Britannica. 2020; 5: 13.
12. Dutschmann M, Dick TE. Pontine mechanisms of respiratory control. Compr Physiol. 2012; 2: 2443-2469.
13. Epstein F, Constantini S. Practical decisions in the treatment of pediatric brain stem tumors. Pediatr Neurosurg. 1996; 24: 24-34.
14. Albright AL. Diffuse brainstem tumors. When is a biopsy necessary. Pediatr Neurosurg. 1996; 24: 252-255.
15. Hansen MHA, Van Vuurden DG, Vandertop WP, et al. Diffuse intrinsic pontine glioma a systematic update on clinical trials and biology. Cancer Treat Rev. 2012; 38: 27-35.
16. Negretti L, Bouchireb K, Levy-Piedbois C, et al. Hypofractionated radiotherapy in the treatment of diffuse intrinsic pontine glioma in children A single institution's experience. J Neurooncol. 2011; 104: 773-777.
17. Lee F. Radiation of infratentorial and supratentorialbrainstem tumors. J Neurosurg. 1975; 43: 65-68.
18. Halperin EC. Pediatric brain stem tumors pattern oftreatment failure and their implications for radiotherapy. Int J Radiat Oncol Biol Phys. 1985; 11: 1293-1298.
19. Eifel PJ, Cassady JR, Belli JA. Radiation therapy of tumorsof the brainstem and midbrain in children experience of the Joint Center for Radiation Therapy and Children's Hospital Medical Center (1971-1981). Int J Radiat Oncol Biol Phys. 1987; 13: 847-852.
20. Freeman CR, Suissa S. Brain stem tumors in children results of a survey of 62 patients treated with radiotherapy. Int J Radiat Oncol Biol Phys. 1986; 12: 1823-1828.
21. Donaldson SS, Laningham F, Fisher PG. Advances toward an understanding of brainstem gliomas. J Clin Oncol. 2006; 24: 1266-1272.
22. Robison NJ, Kieran MW. Diffuse intrinsic pontine glioma A reassessment. J Neurooncol. 2014; 119: 7-15.
23. Mandell LR, Kadota R, Freeman C, et al. There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys. 1999; 43: 959-964.
24. Albright AL. Diffuse brainstem tumors. When is a biopsy necessary. Pediatr Neurosurg. 1996; 24: 252-255.
25. Halperin EC, Wehn SM, Scott JW, et al. Selection of a management strategy for pediatric brainstem tumors. Med Pediatr Oncol. 1989; 17: 116-125.

26. David A Walker, Jonathan A G Punt, Michael Sokal. Clinical management of brain stem glioma. Arch Dis Child. 1999; 80: 558-564.

27. Akiko Hayashi, Eiko Ito, Motoko Omura, et al. Hypofractionated radiotherapy in children with diffuse intrinsic pontine glioma. Pediatr Int. 2020; 62: 47-51.

28. Freeman CR, Krischer J, Sanford RA, et al. Hyperfractionated radiotherapy in brain stem tumors Results of a Pediatric Oncology Group study. Int J Radiat Oncol Biol Phys. 1988; 15: 311-318.

29. Freeman CR, Krischer J, Sanford RA. Hyperfractionated radiation therapy in brain stem tumors. Results of treatment at the 7020 cGy dose level of Pediatric Oncology Group study #8495. Cancer. 1991; 68: 474-481.

30. Freeman CR, Krischer JP, Sanford RA. Final results of a study of escalating doses of hyperfractionated radiotherapy in brain stem tumors in children A Pediatric Oncology Group study. Int J Radiat Oncol Biol Phys. 1993; 27: 197-206.

31. Slotman BJ, Kralendonk TH, Van Alphen HA. Hypofractionated radiationtherapy in patients with glioblastoma multiforme results of treatment and impact of prognostic factors. Int J Radiat Oncol Biol Phys. 1994; 34: 895-898.

32. Jannsens GO, Jannsen MH, Lauwers SJ, et al. Hypofractionation vs conventional radiation therapy for newly diagnosed diffuse intrinsic pontine glioma A matched-cohort analysis. Int J Radiat Oncol Biol Phys. 2013; 85: 315-320.

33. Zaghloul MS. Has hypofractionated radiotherapy become the standard of care in pediatric DIPG. Child's Nerv Syst. 2015; 31: 1221-1222.

34. Hankinson CT, Patibandla MR, Green A, et al. Hypofractionated radiotherapy for children with diffuse intrinsic pontine gliomas. Pediatr Blood Cancer. 2016; 63: 716-718.

35. Zaghloul MS, Eldebawy E, Ahmed S, et al Hypofractionated conformal radiotherapy for pediatric diffuse intrinsic pontine glioma DIPG A randomized controlled trial. Radiother Oncol. 2014; 111: 35-40.

36. Christopher Freese, Vinita Takiar, Maryam Fouladi, et al. Radiation and subsequent reirradiation outcomes in the treatment of diffuse intrinsic pontine glioma and a systematic review of the reirradiation literature. Pract Radiat Oncol. 2017; 7: 86-92.

37. Alvaro Lassaletta, Douglas Strother, Normand Laperriere, et al. Reirradiation in patients with diffuse intrinsic pontine gliomas The Canadian experience. Pediatric Blood Cancer. 2018; 65: e26988.

38. Mark J Amsbaugh, Anita Mahagan, Peter F Thall, et al. D Phase ½ Trial of Reirradiation for Diffuse Intrinsic Pontine Glioma. Climical Investigation. 2019; 104: 144-148.

39. Janssens GO, Gandola L, Bolle S. Survival benefit for patients with diffuse intrinsic pontine glioma DIPG undergoing re-irradiation at first progression A matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group. Eur J Cancer. 2017; 73: 38-47.

40. Zamora PL, Miller SR, Kovoor JJ. Single institution experience in re-irradiation of biopsy-proven diffuse intrinsic pontine gliomas. Childs Nerv Syst. 2021; 37: 2539-2543.

41. Morales La Madrid A, Santa-María V, Cruz Martinez O, et al. Second re-irradiation for DIPG progression re-considering "old strategies" with new approaches. Childs Nerv Syst. 2017; 33: 849-852.